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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/532,447	04/22/2005	Aldo Pinchera	B-0496 PUS	1713
31834 7590 04/29/2008 BRACCO RESEARCH USA INC. 305- COLLEGE ROAD EAST PRINCETON, NJ 08540				
EXAMINER				
RAE, CHARLESWORTH E				
ART UNIT		PAPER NUMBER		
1611				
MAIL DATE		DELIVERY MODE		
04/29/2008		PAPER		

**Please find below and/or attached an Office communication concerning this application or proceeding.**

The time period for reply, if any, is set in the attached communication.

### Office Action Summary

**Application No.**

10/532,447

**Applicant(s)**

PINCHERA ET AL.

**Examiner**

CHARLESWORTH RAE

**Art Unit**

1611

**Period for Reply** -- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

**Status**

- 1) ☒ Responsive to communication(s) filed on 01 February 2008.
- 2a) ☒ This action is **FINAL**. 2b) ☐ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

**Disposition of Claims**

- 4) ☒ Claim(s) 9-15 and 17-25 is/are pending in the application.
- 4a) Of the above claim(s) 1-25 is/are withdrawn from consideration.
- 5) ☐ Claim(s) \_\_\_\_\_ is/are allowed.
- 6) ☒ Claim(s) 9-16, and 25 is/are rejected.
- 7) ☐ Claim(s) \_\_\_\_\_ is/are objected to.
- 8) ☐ Claim(s) \_\_\_\_\_ are subject to restriction and/or election requirement.

**Application Papers**

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on \_\_\_\_\_ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

**Priority under 35 U.S.C. § 119**

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some \* c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
  2. ☐ Certified copies of the priority documents have been received in Application No. \_\_\_\_\_.
  3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

\* See the attached detailed Office action for a list of the certified copies not received.

**Attachment(s)**

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/S5108)
- 4) ☐ Interview Summary (PTO-413)
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: \_\_\_\_\_
- Paper No(s)/Mail Date \_\_\_\_\_

### **DETAILED ACTION**

Applicant's arguments, filed 2/1/08, have been fully considered but they are not deemed to be persuasive. Rejections and/or objections not reiterated from previous office actions are hereby withdrawn. The following rejections and/or objections are either reiterated or newly applied. They constitute the complete set of actions being applied to the instant application.

Applicant's statement requesting rejoinder of the method claims upon allowance of the product claims is acknowledged and made of record.

This action is made final

### **Status of the Claims**

Claims 9-15 and 17-25 are currently pending in this application.

Claims 17-25 are withdrawn for being directed to non-elected subject matter.

Claims 9-15 and 25 are under examination.

### **Amendment to the Specification**

Receipt of the clean copy of the amendment to the specification is acknowledged.

### **Restriction**

Applicant request the withdrawal of restriction requirement because 1) Group I and Group II can be searched together and 2) searching said groups would not create an undue search burden on the examiner.

In response, the restriction regarding Groups I and II is withdrawn.

### **Exhibit I**

Receipt and consideration of Exhibit 1 is duly noted.

**Response to applicant's arguments/remarks**

Rejection under 112, 2nd para

This rejection is withdrawn in view of the amendment.

Rejection under 103(a)

Applicant contends that this rejection should be withdrawn for essentially the following summarized reasons (see applicant's Response, received 2/1/08, at pages 6-10):

1) Lopresti does not disclose oral administration of T3S. Rather, Lopresti confirms the expectation of the skilled artisan that T3S would not be absorbed by the GI tract given that it bears the highly polarized/ionic group – OSO<sub>3</sub>H. Lopresti concluded no absorption of intact (labeled) T3S was detected following oral ingestion. Thus, Lopresti teaches away from the claimed invention.

2) Applicant note that 1  $\mu$ Ci does not correspond to 1 microgram as a  $\mu$ Ci is a measurement of radioactivity, while a  $\mu$ g is a measurement of weight. Fisher teaches that 1 microgram of a labeled substance emits a given amount of radiation expressed in micro curies; however, this does not mean that 1  $\mu$ Ci corresponds to 1 microgram

3) Contrary to the examiner's opinion, the teaching of Lopresti in combination with Fisher does not suggest an oral composition of T3S at a dose ranging from 5 to 1000  $\mu$ g as claimed.

4) The secondary references of Herfindal and Mol do not cure the deficiencies of the primary references.

5) The instant claimed composition must be regarded as unpredictable and unexpected in view of the prior art.

In response, the rejection is maintained as applicant's arguments and experimental evidence submitted via Exhibit 1 are not found to be sufficient to overcome the rejection for the reasons made of record in the Office action, mailed 11/2/07, at pages 8-11 and for the additional reason:

a) Applicant's assertion that the instant claimed composition must be regarded as unpredictable and unexpected in view of the prior art lacks support as evidenced by the teaching of Bunevicius et al. of triiodothyronine 12.5 µg/capsule administered alone (Bunevicius et al. Effects of thyroxine as compared with thyroxine plus triiodothyronine in patients with hypothyroidism. New England Journal of Medicine. 1999; 340(6):424-429; electronic pages 1-12) and the teaching of Miura et al. ( US Patent 5,11,6828; col. 5, line 61 to col. 6, line 49) of formulations comprising L-triiodothyronine 0.0123 mg in combination with ethinylestradiol 0.02 mg, lactose proper quantity, total 300 mg/capsules (col. 6, lines 32-48).

b) It is the examiner's position that dosage limitations recited in claims 9-13 constitute dose optimization as evidenced by the teaching of Bunevicius et al. of thyroxine doses of 50 to 300 µg/day (page 3, Study Protocol section, and page 7, first para) and triiodothyronine 5-150 µg/day taught by Miura et al. (col. 3, lines 1-4).

#### **REJECTIONS**

**Claim rejections – 35 USC 103(a)**

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

(a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negated by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 9-15 and 25 are rejected under 35 U.S.C. 103(a) as being unpatentable over Lopresti et al. ("Characteristics of 3,5,3'-Triiodothyronine Sulfate Metabolism in Euthyroid Man", Journal of Clinical Endocrinology and Metabolism, Vol. 73, No. 4, 1992, pages 703-709, item "CA" on PTO 1449 filed on 02/14/2006; already made of record, in view of Mol et al., in view of Herfindal et al. (Herfindal et al. In: Clinical Pharmacy and Therapeutics. 1992, pages 289-291), and in further view of Fisher et al. (US Patent 4254095).

The Rejection made of record in the Office action, mailed 11/2/0, at pages 8-11 is incorporated by reference.

Based on the teaching of Mol et al. that the availability of large quantities of pure iodothyronine sulfates and sulfamates should facilitate the study of the importance of sulfate conjugation in the metabolism of thyroid hormone, someone of skill in the art would have been motivated to combine the teachings of the above cited references to create the instant claimed inventive concept.

Thus, someone of skill in the art at the time the instant invention was made would have deemed it obvious to create the instant claimed invention with reasonable predictability.

#### **Relevant Art of Record**

The below art made of record and relied upon are considered pertinent to applicant's invention.

Salhanick et al. (US Patent Application Pub. No. 2002/0076827) teach a method of diagnosing a thyroid condition in a subject which comprises: a) obtaining a suitable urine sample from the subject; b) determining the concentration of triiodothyronine sulfate in the sample by a method which is not a radioimmunoassay; and c) comparing the concentration of triiodothyronine sulfate with a urinary concentration of triiodothyronine sulfate in a normal subject; wherein i) a concentration of triiodothyronine sulfate which is lower than the urinary concentration of triiodothyronine sulfate in the normal subject diagnoses hypothyroidism in the subject; and ii) a concentration of

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triiodothyronine sulfate which is higher than the urinary concentration triiodothyronine sulfate of in the normal subject diagnoses hyperthyroidism in the subject (para 0054).

Bunevicius et al.(Bunevicius et al. Effects of thyroxine as compared with thyroxine plus triiodothyronine in patients with hypothyroidism. New England Journal of Medicine. 1999; 340(6):424-429; electronic pages 1-12) disclose study data showing that administration of thyroxine 50 µg/tablet plus triiodothyronine 12.5 µg/capsule per day was found to be superior than administration of thyroxine alone in patients with hypothyroidism (page 3, Study Protocol section; and page 7, Discussion section). Bunevicius et al. disclose doses of thyroxine of 50 to 300 µg (page 3, Study Protocol section, and page 7, first para).

Miura et al. exemplify formulations comprising L-triiodothyronine 0.0123 mg in combination with ethinylestradiol 0.02 mg, lactose proper quantity, total 300 mg/capsules (col. 6, lines 32-48). Miura et al. also teach L-thyroxine 0.05 mg, estriol 0.5 mg, corn starch 40 mg, magnesium stearate 10 mg, lactose proper quantity, total 250 mg/tablet (col. 6, lines 32-43). Miura et al. teach that in a study, the group of patients who received thyroid hormone in combination with an estrogen were found to have X-ray radiography showed a more remarkable increase in bone amount than in the group administered with the estrogen alone (col. 4, lines 1-58; and col 5, lines 39-46). Miura et al. teach L-thyroxine in doses of 25-400 µg/day, and L-triiodothyronine 5-150 µg/day. See col. 3, lines 1-4. Miura et al. teach that the effective ingredients in the composition may be used in the form of pharmaceutically acceptable salts thereof and



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may also be formulated together with other pharmaceutically active components (col. 5, line 61 to col. 6, line 49).

**THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire **THREE MONTHS** from the mailing date of this action. In the event a first reply is filed within **TWO MONTHS** of the mailing date of this final action and the advisory action is not mailed until after the end of the **THREE-MONTH** shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than **SIX MONTHS** from the date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Charlesworth Rae whose telephone number is 571-272-6029. The examiner can normally be reached between 9 a.m. to 5:30 p.m. Monday to Friday.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Michael Woodward, can be reached at 571-272-8373. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR.

Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have any questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 800-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

20 April 2008

/C. R./

Examiner, Art Unit 1611

/Brian-Yong S Kwon/

Primary Examiner, Art Unit 1614